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Editorial Comment

Do Neutrophils Mediate the Phenomenon of Stunned Myocardium?*

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Brief periods of transient ischemia have been associated with prolonged postischemic dysfunction—the syndrome of stunned myocardium (1). In the canine model of 15 min of coronary artery occlusion followed by reperfusion, recovery of function may require hours to days despite the absence of tissue necrosis (2,3). Biochemical abnormalities have been observed in stunned myocardium: subendocardial adenosine triphosphate (ATP) levels are reduced for at least 3 days after reperfusion of a coronary artery subjected to 15 min of occlusion (4). Stunned myocardium has been observed in patients receiving thrombolytic therapy for acute evolving myocardial infarction, as well as in patients undergoing exercise stress testing (5).

Mechanisms of myocardial stunning. There have been several proposed mechanisms for the phenomenon of stunned myocardium, including altered calcium flux, oxygen free radical damage and abnormal energy utilization (6). Oxygen free radicals have been implicated as a cause of stunned myocardium by a number of investigators (7–9). These cytotoxic species such as superoxide anion and hydroxyl radical are known to be generated during ischemia and reperfusion (10). Oxygen free radicals recently have been documented in the coronary vein effluent of a canine model of 15 min of ischemia and reperfusion by utilizing electron paramagnetic resonance spectroscopy and a spin-trapping agent (10). In addition, oxygen radicals have been shown to inhibit the function of isolated sarcolemmal membrane preparations (11) and to depress function of isolated papillary muscle preparations (12). Several independent laboratories (7–9,10) including our own (8) have observed that administration of oxygen free radical scavengers, such as superoxide dismutase plus catalase, enhances the return of function of myocardium subjected to 15 min of ischemia followed by reperfusion. This beneficial effect appears to occur without any improvement in ATP content of the tissue (8). Thus, oxygen free radicals do appear to play a role in the pathogenesis of stunned myocardium induced by brief periods of ischemia and reperfusion.

What is the origin of oxygen free radicals during ischemia and reperfusion? The xanthane oxidase reaction, neutrophils and electron transport chain of mitochondria are some of the potential sources (13,14). Perhaps the most controversial source associated with brief periods (15 min or less) of ischemia and reperfusion is the neutrophil. One problem with the concept that neutrophils are important in this setting is that their presence has not been described by histologic or electron microscopic examination in models of reversible ischemia (15). In fact, a recent indium-labeling study failed to document neutrophil influx into myocardium of dogs subjected to 12 min of ischemia and reperfusion (16).

Comparison with previous studies. Engler and Covell (17), however, showed that leukopak filtration of neutrophils from coronary reperfusate could blunt the phenomenon of stunned myocardium during brief periods of ischemia and reperfusion. In a preliminary report, Westlin and Mullane (18), also utilizing leukopak filtration, showed a transient improvement of stunned myocardium in neutropenic dogs. However, O'Neill et al. (19) showed that when neutrophils were suppressed with antiserum there was no effect on stunned myocardium. The present study by Jeremy and Becker (20) in this issue of the Journal used techniques similar to those of Engler and Covell (17) but the findings support the concept that neutrophils are not important in causing myocardial stunning in a model of brief coronary occlusion not associated with necrosis. The study is consistent with the data of O'Neill et al. (19) and with reported data that did not identify neutrophil infiltration into reversibly injured myocardium (15). The data are also consistent with models of isolated hearts that are known to develop stunning after global ischemia or hypoxia in which buffers devoid of neutrophils are used as the coronary perfusate but in which oxygen radical scavengers appear to be protective (21).

There are, however, some differences between the present study (20) and that of Engler and Covell (17); the latter suggested that very few neutrophils may be needed to cause stunning. Engler and Covell (17) therefore filtered neutrophils from blood entering both the left anterior descending and circumflex coronary arteries, whereas Jeremy and Becker (20) filtered only that blood entering the left anterior descending artery. Thus, in the study by Jeremy and Becker (20) neutrophils from the nonoccluded circumflex bed might have entered the bed of the left anterior descending coronary artery from collateral vessels, resulting in stunning. This occurrence would not explain the results of

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O'Neill et al. (19) in which systemic neutropenia did not prevent stunning. It also would not explain a recent report by Schott et al. (22) in which myeloperoxidase activity (a marker of neutrophils) within stunned myocardium was similar to that of nonischemic controls. Furthermore, in that study, administration of antibody to the "adhesion-promoting" Mol glycoprotein on neutrophils did not prevent stunned myocardium.

The exact reasons for the differences in results among these studies is not clear. There may be as yet unknown or subtle factors that contribute to stunning. For example, the state of activation rather than the number of neutrophils present in the myocardium may be a crucial factor. Myers et al. (23) recently showed that neutrophils activated by phorbol myristate acetate depressed myocardial function and increased coronary vascular resistance in an isolated perfused rabbit heart model; unactivated neutrophils did not show this phenomenon. Also, R. Engler (personal communication, 1988) has suggested that other factors, such as the amount of vitamin E in diets of these animals, might help explain differences in results among laboratories.

Role of neutrophils. Although Jeremy and Becker's present study (20) shows that neutrophils do not play a role in causing stunning of the myocardium during brief periods of ischemia and reperfusion, neutrophils may play a more important role during prolonged periods (>1 h) of ischemia followed by reperfusion as might occur in the clinical situation of patients receiving thrombolytic therapy plus reperfusion for evolving acute myocardial infarction. Neutrophil infiltration has been observed on histologic (24,25), as well as by indium labeling early after reperfusion of irreversibly injured myocytes (26). We have observed zones of myocardium subjected to only a few hours of ischemia and reperfusion in which extensive neutrophil infiltration was present within the myocardium (24). Thus, while the early classic pathologic studies (27) suggested that neutrophil infiltration did not peak until 48 h after infarction, these studies were performed before the era of coronary reperfusion for the treatment of acute infarction. Coronary reperfusion may accelerate the early inflammatory response after infarction.

Engler et al. (28) have shown that the neutrophils may cause plugging of the microvasculature and contribute to the "no reflow" phenomenon in a model of prolonged occlusion (28). Some studies (25,29–31) have suggested that suppression of neutrophils in models of coronary occlusion with and without reperfusion may reduce myocardial infarct size and these studies have implicated the neutrophils as a cause of so-called reperfusion injury. Whether neutrophils contribute to stunned myocardium of peri-infarct areas in models of prolonged ischemia followed by reperfusion remains to be determined.

Finally, a word of caution. Neutrophils are a key element of the early inflammatory reaction that occurs after acute myocardial infarction. This early inflammatory reaction is the first step in the healing process. Interventions that suppress neutrophils conceivably could alter the way in which myocardial infarcts heal. In fact, a host of anti-inflammatory agents, when administered shortly after coronary occlusion, have been shown to result in delayed healing, thin-walled scars and exacerbation of myocardial infarct expansion (32–34). However, one recent study (35) showed that administration of the oxygen free radical scavenger superoxide dismutase to reperfused infarcts did not result in excessive thinning of the infarcted ventricular wall.

Conclusions. The study by Jeremy and Becker (20) supports the concept that neutrophils do not play a role in postischemic ventricular dysfunction of myocardium that has been subjected to a brief period of ischemia and reperfusion not associated with necrosis. This study, however, does not rule out the possibility that neutrophils are important in models of more prolonged ischemia associated with irreversible cell injury. In fact, a preliminary study from the same research group (36) showed that perfusion of neutrophil-free blood after a 90 min period of ischemia reduced myocardial infarct size.

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